REMARKS

The February 4, 2008 Official Action and the references cited therein have been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, a shortened statutory response period of three (3) months was set forth in the February 4, 2008 Official Action. Therefore, the initial due date for response was May 4, 2008. Accordingly, a petition for a 2 month extension is presented with this response, which is being filed within the two month extension period.

The Examiner has rejected claims 38, 39, and 41-47 for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

Claims 38, 39, and 41-47 have also been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent Application Publication No. 2001/0001040 in view of U.S. Patent 5,922,689.

The foregoing rejections constitute all of the grounds set forth in the February 4, 2008 Official Action for refusing the present application.

In accordance with the instant amendment, claims 53 and 43 have been added. Support for new claims 53 and 54 can be found throughout the specification including, for example, in original claim 41. No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the present amendment and the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §112, first paragraph rejection of claims 38, 39, and 41-47 and the 35 U.S.C. §103(a) rejection of claims 38, 39, and 41-47, as set forth in the February 4, 2008 Official Action, cannot be maintained. These grounds of rejection are, therefore, respectfully traversed.

CLAIMS 38, 39, AND 41-47 SATISFY THE ENABLEMENT REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected claims 38, 39, and 41-47 for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. It is the Examiner's position that while the specification is enabling for the treatment of breast cancer, the specification does not reasonably provide enablement for the treatment of other cancers.

Applicants respectfully disagree with the Examiner's position. Applicants submit herewith Hou et al. (Cancer Res. (2007) 67:792-801), Kumar et al. (J. Med. Chem. (2008) 51:1706-1718), Muller et al. (Nature Med. (2005) 11:312-319), and a Declaration by co-inventor Dr. George C. Prendergast (hereinafter the Prendergast Declaration) which provide evidence of the effectiveness of the instantly claimed compounds against several different cancer types. Specifically, the effectiveness of the administration of an IDO inhibitor and a chemotherapeutic agent against melanomas, breast cancers, lung cancers, and colon cancers are demonstrated. In light of this broad range of efficacy, Applicants respectfully submit that the instantly claimed methods of treating cancer are fully enabled.

Example 4 of the instant application of the instant application demonstrates the effectiveness of the administration of an IDO inhibitor in combination with a chemotherapeutic agent. Indeed, Table 1 and Figures 5 and 11 clearly demonstrate a dramatic reduction in tumor volume in a breast cancer model when both an IDO inhibitor and a chemotherapeutic agent are used. The average tumor volume of the untreated mouse increased 195.1% in the experiments described in Example 4. The administration of the IDO inhibitor 1-methyl-DL-tryptophan alone reduced the average increase in tumor volume to 80.27%. The administration of either the chemotherapeutic agent paclitaxel (Taxol®) or the chemotherapeutic agent cisplatin individually was less effective and only reduced the average increase in tumor

volume to 139.4% and 91.35%, respectively. In stark contrast, the administration of the IDO inhibitor 1-methyl-DL-tryptophan in combination with either the chemotherapeutic agent paclitaxel or cisplatin yielded a dramatic ***reduction*** in tumor volume, not just a slowing in the increase in tumor volume. Indeed, the administration of 1-methyl-DL-tryptophan with paclitaxel led to a 30.2% reduction in tumor volume and the administration of 1-methyl-DL-tryptophan with cisplatin led to a 28.0% reduction in tumor volume. Thus, Example 4 clearly demonstrates the effectiveness of the instantly claimed method against breast cancers.

Hou et al. also demonstrate the effectiveness of the instantly claimed invention against melanomas and another breast cancer. For example, Figure 1A clearly demonstrates that the administration of 1-methyl-DL-tryptophan and the chemotherapeutic agent cyclophosphamide (black squares) resulted in a dramatic reduction in tumor volume. Notably, the administration of either 1-methyl-DL-tryptophan alone or cyclophosphamide alone did not yield a significant reduction in melanoma tumor volume 4 weeks after administration. However, the co-administration of 1-methyl-DL-tryptophan and cyclophosphamide led to a large decrease in tumor volume compared to controls and the administration of either compound individually (P value of < 0.05).

Figure 2 of Hou et al. also demonstrates that the combined administration of a chemotherapeutic agent and an IDO inhibitor is effective against the 4T1 breast tumor model. Again, the administration of a chemotherapeutic agent (paclitaxel or cyclophophamide) alone had little effect on the breast tumor volume and only slightly retarded tumor growth. However, the co-administration of 1-methyl-DL-tryptophan in combination with paclitaxel resulted in a dramatic reduction in the breast tumor volume.

Kumar et al. demonstrate the effectiveness of the co-administration of the IDO inhibitor vitamin K3 with the chemotherapeutic agent paclitaxel. Indeed, Figure 2B

demonstrates that the administration of paclitaxel or vitamin K3 alone only slows the growth of breast tumors. In contrast, the administration of both vitamin K3 and paclitaxel caused a *reduction* in breast tumor volume.

Further, Muller et al. demonstrate the effectiveness of the co-administration of the IDO inhibitor methyl-thiohydantoin-tryptophan (methyl-TH-trp) with the chemotherapeutic agent paclitaxel against breast cancer. Figure 6 demonstrates that the administration of paclitaxel or methyl-TH-trp alone only slows the growth of breast tumors. In contrast, the administration of both methyl-TH-trp and paclitaxel caused a *reduction* in breast tumor volume.

The Prendergast Declaration, as evidenced by Exhibits A and B, also establishes that the administration of an IDO inhibitor and a chemotherapeutic agent is effective against lung cancers and colon cancers. First, as evidenced by the data provided in Exhibit A, the administration of the IDO inhibitor 1-methyl-D-tryptophan (see, e.g., Hou et al., particularly Figure 3) in combination with cyclophosphamide dramatically reduced lung tumor volume growth compared to controls and the administration of either 1-methyl-D-tryptophan or cyclophosphamide individually. Second, as evidenced by the data provided in Exhibit B, the administration of 1-methyl-D-tryptophan in combination with cyclophosphamide dramatically reduced colon tumor volume growth compared to controls and the administration of either 1-methyl-D-tryptophan or cyclophosphamide alone.

In view of all of the foregoing, Applicants have demonstrated the effectiveness of the administration of an IDO inhibitor and a chemotherapeutic agent against a variety of cancers including a melanoma, two breast cancers, a colon cancer, and a lung cancer. None of the cancers tested have been found to be resistant to the instantly claimed treatment. In light of the broad range of efficacy, Applicants respectfully submit that the instantly claimed methods of treating cancer are fully enabled. Furthermore, any

experimentation required of the skilled artisan to practice the instantly claimed methods of treating a cancer in a patient would not be undue in view of the demonstrated effectiveness of the recited compounds against such a wide range of tumors.

Applicants also note that §2164.08(b) of the MPEP states that:

> "The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

Therefore, even if the instantly claimed methods were ineffective against one particular cancer - which Applicants **strenuously** dispute as the use of an IDO inhibitor and a chemotherapeutic agent has proven effective against all cancers tested - Applicants respectfully submit that the claimed methods would still be sufficiently enabled to satisfy 35 U.S.C. §112, first paragraph.

In view of the foregoing, Applicants respectfully submit that the rejection of claims 38, 39, and 41-47 under 35 U.S.C. §112, first paragraph is untenable and should be withdrawn.

CLAIMS 38, 39, AND 41-47 ARE NOT RENDERED OBVIOUS BY THE '040 APPLICATION IN VIEW OF THE '689 PATENT

Claims 38, 39, and 41-47 have also been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the '040 application in view of the '689 patent. The Examiner contends that the '040 application discloses that IDO inhibitors such as 1-methyl-DL-tryptophan are useful in the treatment of cancer. Further, the '689 patent allegedly discloses that cisplatin is a chemotherapeutic agent which is effective in inhibiting the growth of human breast cancer. The Examiner contends that "it is *prima facie* obvious to combine two

compositions each of which is taught by the prior art to be useful for the very same purpose."

Applicants respectfully disagree with the Examiner's position. The MPEP at §716.02 clearly indicates that the demonstration of greater than expected results are evidence of nonobviousness. Indeed, a "property which makes a [compound] unexpectedly suited for a specific, important utility … can be the basis for overcoming a *prima facie* case of obviousness." Ex parte A, 17 U.S.P.Q.2d 1716 (Fed. Cir. 1990). Further, "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness … of the claims at issue." In re Corkill, 226 U.S.P.Q. 1005 (Fed. Cir. 1985). Additionally, "evidence that a compound is unexpectedly superior in one of a spectrum of common properties … can be enough to rebut a *prima facie* case of obviousness." In re Chupp, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness. See, e.g., In re Albrecht, 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975).

As stated hereinabove, in response to the enablement rejection, Applicants have clearly demonstrated the unexpected superiority of the co-administration of an IDO inhibitor with a chemotherapeutic agent over the administration of either compound alone. Indeed, the effect of the co-administration is substantially greater than the combined effects of the compounds administered individually. For example, Figure 11 of the instant application demonstrates that the administration of 1-methyl-DL-tryptophan, paclitaxel, or cisplatin alone only mildly slowed the growth of the breast cancer. In stark contrast, the co-administration of 1-methyl-DL-tryptophan with paclitaxel or 1-methyl-DL-tryptophan with cisplatin caused the tumor to shrink. This is an unexpectedly superior result with significant benefits and positive implications for the treatment of cancer.

The data provided in Huo et al. also demonstrates the

unexpectedly superior results obtained from the co-administration of an IDO inhibitor with a chemotherapeutic agent. Indeed, the melanoma tumor volume observed in mice treated with either 1-methyl-DL-tryptophan or cyclophosphamide alone is the same after 28 days as mice who received no treatment at all. Again, in stark contrast, the co-administration of 1-methyl-DL-tryptophan with cyclophosphamide reduced the melanoma tumor volume by almost 70% compared to untreated animals (Figure 1A). Figure 2A of Huo et al. also demonstrates that 1-methyl-DL-tryptophan alone did not significantly reduce breast tumor size and cyclophosphamide administered alone only mildly reduced the breast tumor size. In contrast, co-administration of 1-methyl-DL-tryptophan and cyclophosphamide reduced the breast tumor to an undetectable size. Similar results were obtained with another breast cancer and the co-administration of 1-methyl-DL-tryptophan and paclitaxel (Figure 2B).

Additionally, the data provided in Kumar et al. also demonstrates the unexpectedly superior results obtained from the co-administration of an IDO inhibitor with a chemotherapeutic agent. Figure 2B of Kumar et al. shows that the administration of 1-methyl-DL-tryptophan or paclitaxel alone only slightly slowed the growth of breast cancer. In stark contrast, the co-administration of 1-methyl-DL-tryptophan with paclitaxel caused the tumor to shrink dramatically.

Muller et al. also clearly demonstrate the unexpectedly superior results obtained from the co-administration of an IDO inhibitor with a chemotherapeutic agent. As stated hereinabove, Figure 6 of Muller et al. shows that the administration of methyl-TH-trp or paclitaxel alone only slightly slowed the growth of breast cancer. In stark contrast, the co-administration of methyl-TH-trp with paclitaxel caused the tumor to shrink significantly.

The evidence provided with the Prendergast Declaration also demonstrates that while the administration of 1-methyl-D-

tryptophan or cyclophosphamide alone slightly reduced the growth of lung tumors, the co-administration of 1-methyl-D-tryptophan and cyclophosphamide essentially completely inhibited lung tumor growth. Similar results were obtained also obtained for colon tumors.

In view of all of the foregoing, it is without question that the co-administration of an IDO inhibitor with a chemotherapeutic agent produces unexpectedly superior results in terms of inhibiting tumor growth and, therefore, the treatment of cancer. While certain IDO inhibitors are exemplified hereinabove, the unexpectedly superior results have been observed with other IDO inhibitors.

Applicants also note that the MPEP at §2145 states:

> When considering whether proffered evidence is commensurate in scope with the claimed invention, Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition. See, e.g., *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a prima facie case of obviousness. Id.
>
> For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a prima facie case of obviousness if a skilled artisan "could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof." *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof.)

In view of all of the foregoing, Applicants respectfully submit that the rejection of claims 38, 39, and 41-47 under 35 U.S.C. §103(a) is untenable and request its withdrawal.

CONCLUSION

In view of the amendments presented herewith, the foregoing remarks, and the submitted Declaration, it is respectfully urged that the rejections set forth in the February 4, 2008 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to call the undersigned at the phone number given below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
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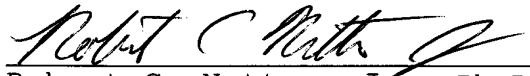
By 
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Enclosure: Hou et al., Cancer Res. (2007) 67:792-801
Kumar et al., J. Med. Chem. (2008) 51:1706-1718
Muller et al., Nature Med. (2005) 11:312-319
Declaration by George C. Prendergast
Exhibits A and B